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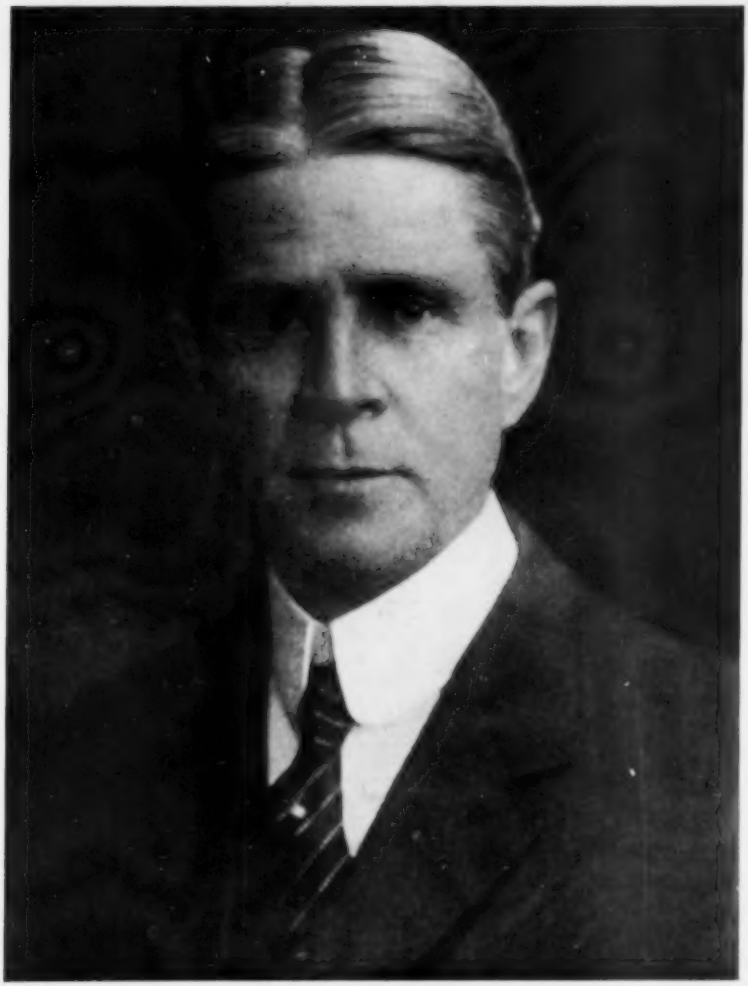
September 1959



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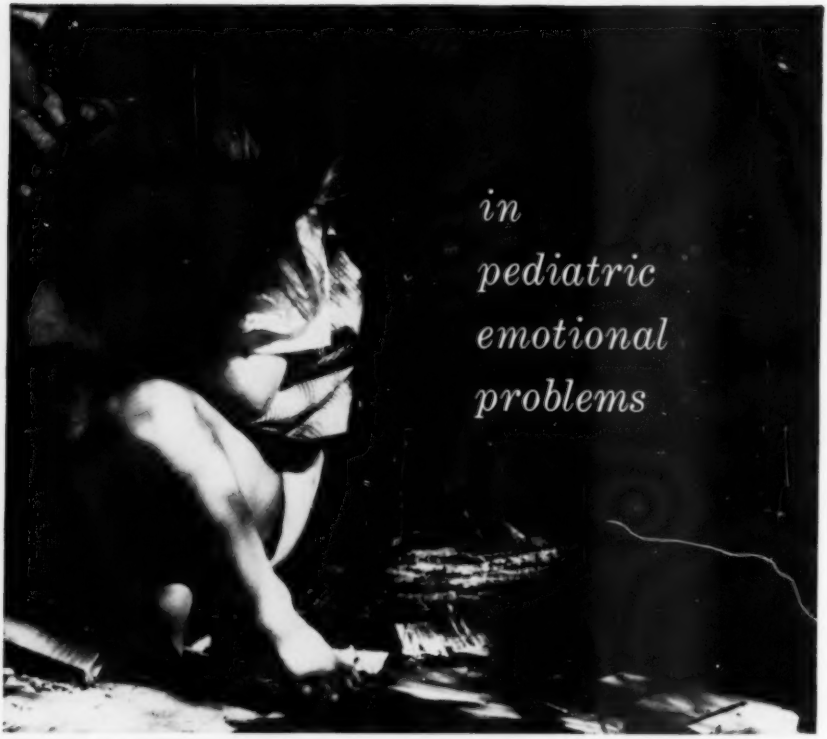

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Vol. 76, No. 9

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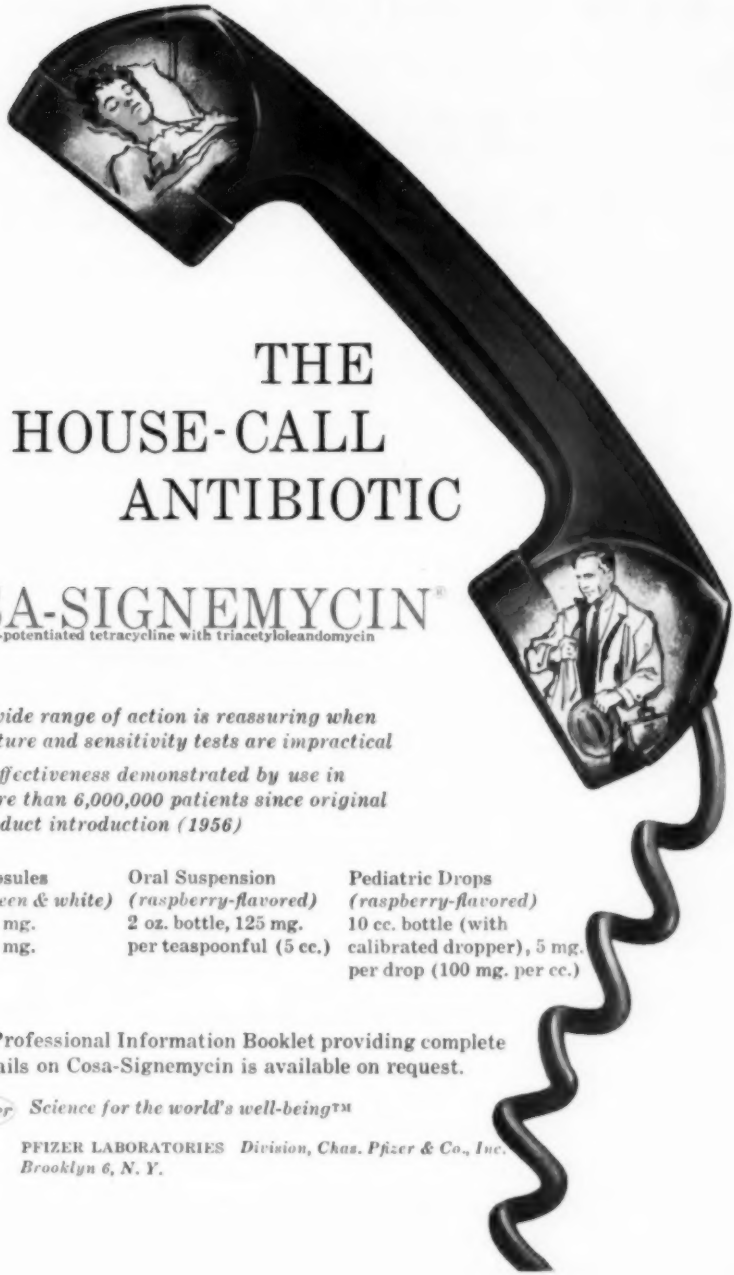

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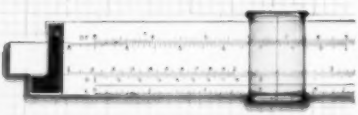

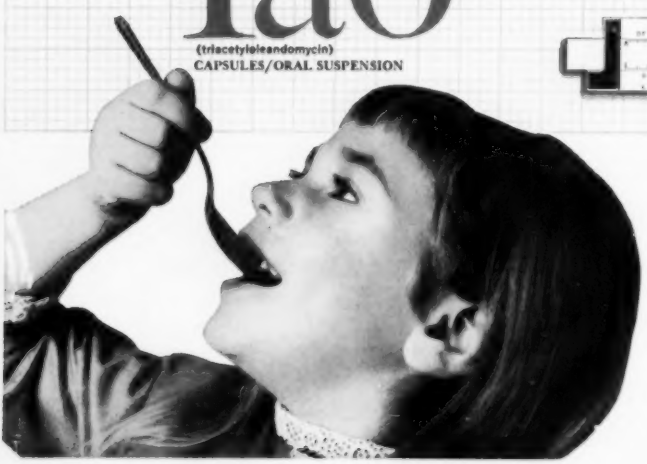

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As is well known, Doctor Holt left his mark on a host of extremely able young men who themselves later rose to great eminence in the pediatric world. It is said that while teaching at the College of Physicians and Surgeons, his sessions at Vanderbilt Clinic and Babies Hospital took on characteristics of formal lectures for medical students in the College amphitheatre.

Archives cannot attempt to enhance the wealth of words which so effectively memorialize the richness of quality of his lasting contributions. But it does chronicle the fact that Doctor Holt was one of this journal's original editors. With pride therefore, *Archives* presents his portrait and this commemorative appreciation.

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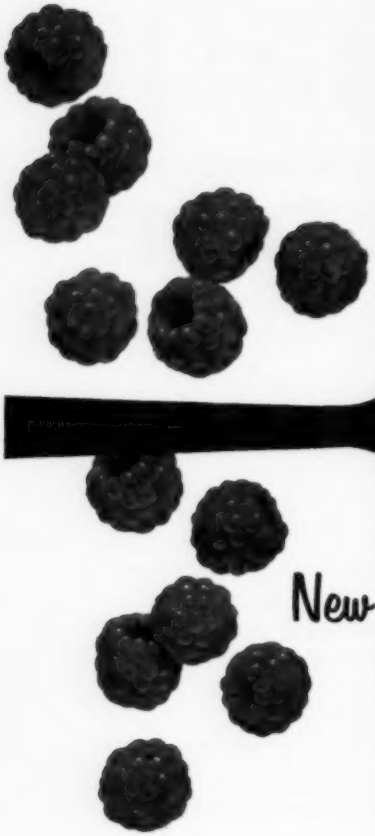

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September 1959
Vol. 76 No. 9

MICROMELIA WITH TETRALOGY OF FALLOT

ROBERT H. WHITTLESEY,* M.D., F.A.C.S.

Cleveland, Ohio

Taussig, in her excellent treatise on congenital malformations of the heart[1], states that "abnormalities of the direction in which the aorta arches, and in the origin of the great vessels from the aortic arch, are by no means rare." Potter, in her equally studious volume devoted to the pathology of the foetus and newborn[2], mentions that "the malformations that may be found in the extremities are legion." Recently an unusual combination of such embryological defects was encountered: a white male child with virtual absence of the left arm, together with tetralogy of Fallot, a right aortic arch, and anomalies of the great vessels. Examination of the foregoing and other pertinent literature [3-6] has revealed no precedent for this case herein described. The report is published, then, because of its unusual nature, and also because consideration of the unique combination of deformities has led to a theoretical cause-and-effect relationship between the vascular anomalies and failure of the limb to develop in normal fashion.

CASE PRESENTATION

S. F., a four year old white male, was the product of a normal pregnancy and delivery. He was born with a rudimentary left upper extremity (see Fig. 1). He was cyanotic from the time of birth. At 3 months he was admitted to another hospital for evaluation. It was felt that the cardiac anomaly was not amenable to surgery.

In spite of a normal birth weight the child developed slowly. No serious illness occurred, however, to the time of his second hospitalization. He had one sister two years his elder, normal in all respects.

At age 4, S. F. was admitted for re-evaluation. At this time,

* Clinical Assistant Surgeon (Pediatric), Dep't. of Surgery, St. Luke's Hospital.
* Clinical Instructor in Surgery, School of Medicine, Western Reserve University, Cleveland, Ohio.

when we first saw him, he weighed 10 kilograms. He could stand alone, but had never learned to walk. Mother stated that until one year prior to this time, he had frequent episodes of loss of consciousness, during which his eyes rolled upward, he became limp and intensely cyanotic, but had no convulsions. During the first two years of life especially, he had several such episodes daily.

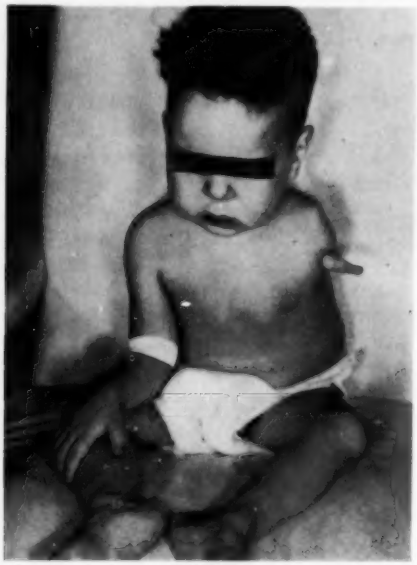

FIG. 1

Absence deformity of the left upper extremity. Left arm is represented by this vestigial ray which contained two small rudimentary bones, and had a normal nail at the tip. Note asymmetry of face.

Physical examination revealed a small boy (Fig. 1) poorly developed, but in a good state of nutrition. Dentition was extremely poor, the flesh soft and flabby. His head was slightly flattened and asymmetrical. There was cyanosis of all warm surfaces and skin. The fingers and toes were clubbed. The left chest bulged; there was a systolic thrill in the 3rd and 4th left intercostal spaces. P_2 was of least normal intensity, probably not split. There was a harsh, rasping, rough, grade III systolic murmur maximal in the area of the thrill. No diastolic murmur was heard. The heart appeared to be enlarged to the left. Femoral pulses were normal. The lung fields were clear; the liver and spleen of normal size.

A cardiac consultation was obtained. Chest roentgenograms and fluoroscopy showed an enlarged heart, with an enlarged right

ventricle and arium. It was stated that pulsations in the right and left pulmonary artery were decreased, as were the lung markings. The aortic arch appeared to be on the right, but it was felt that this could not be confirmed or disproved completely by the roentgenograms with barium in the esophagus. Samples of the electrodiogram which was first obtained showed evidence of marked right ventricular hypertrophy (see Fig. 2).

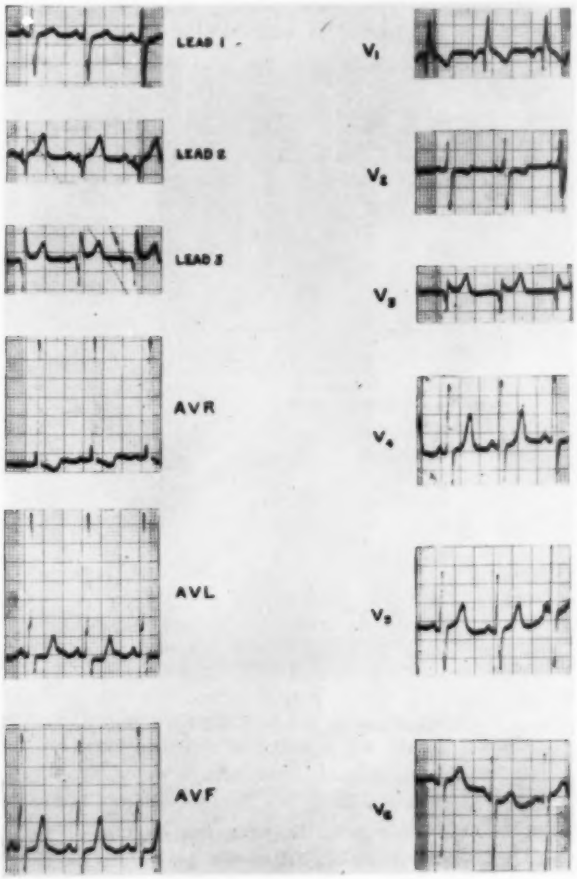

FIG. 2

Electrocardiographic interpretation: "Normal sinus rhythm, abnormal right axis deviation, right ventricular hypertrophy".

Cardiac catheterization was performed (Fig. 3). Angiocardiograms showed a definite right to left shunt. A phonocardiograph was also obtained (see Fig. 4), and the heart sounds were recorded on electrosensitive tape.

In the week following cardiac evaluation, the child developed several episodes of acute anoxia, similar to those described by the mother, and which had not occurred for over a year. These were alleviated by morphine, oxygen, and placing the patient in an "horizontal squatting position," i.e. placing him prone with legs drawn up under the trunk. It was decided to attempt surgical relief by use of a shunting procedure. The pre-operative diagnoses were: tetralogy of Fallot, right aortic arch and right descending aorta; micromelia, left upper extremity; facial dysostosis.

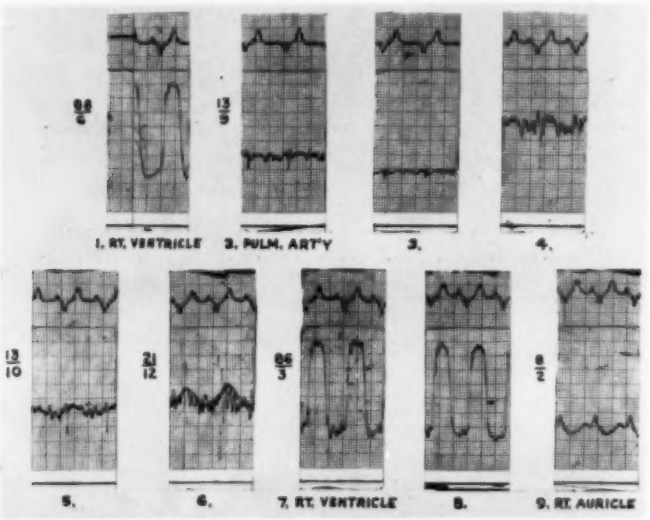

FIG. 3

Record of cardiac catheterization. Evidence was present of an infundibular type of pulmonary stenosis and a marked left to right intracardiac shunt.

OPERATION

The right chest was entered in the fourth interspace. Lobes of the right lung were retracted and dissection of the mediastinum commenced. A right aortic arch was found; there was a marked thrill over the base of the pulmonary artery. Due to an obvious

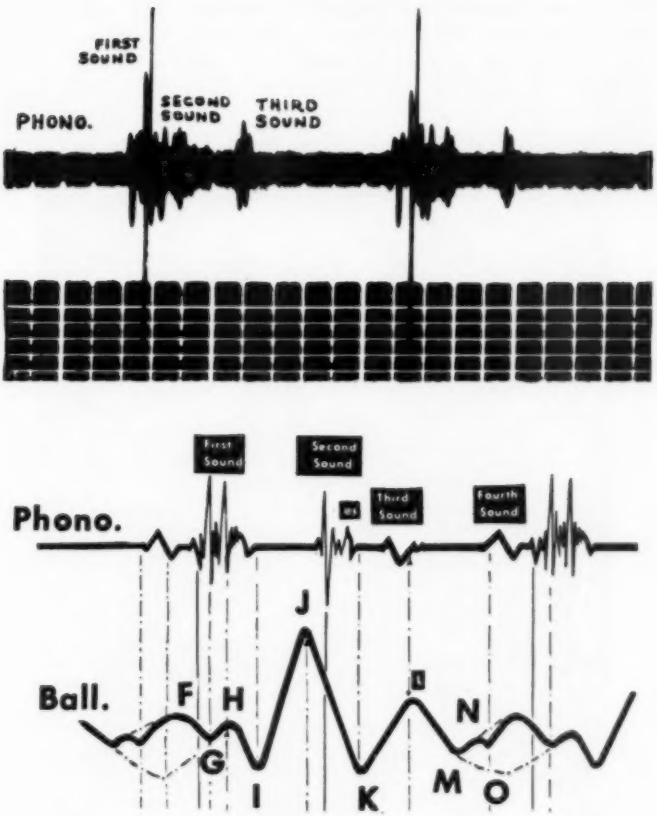

FIG. 4

Phonocardiographic tracing from this patient, in comparison with diagram of normal heart sounds. Note evidence of murmur at point "x".

anomaly of the main branches off the arch, the nature of which was difficult to determine, the pericardium was opened; diagnosis of tetralogy of Fallot was confirmed. In the presence of the single right normal upper extremity, and with continued difficulty in determining the exact nature of the aortic arch anomaly, it was decided to attempt anastomosis of right pulmonary artery to aorta. It was feared that division of the right subclavian artery for a Blalock procedure might impoverish the arterial flow to the right

arm, should insufficient collaterals be available. The pulmonary-aortic anastomsis was completed as the child's condition deteriorated. Although an adequate anastomosis, with a 4.3 mm. slit in the aorta, was obtained, the shunt did not appear to function well; only a feeble thrill was felt. There was considerable angulation of the right pulmonary artery when the lung was re-expanded.

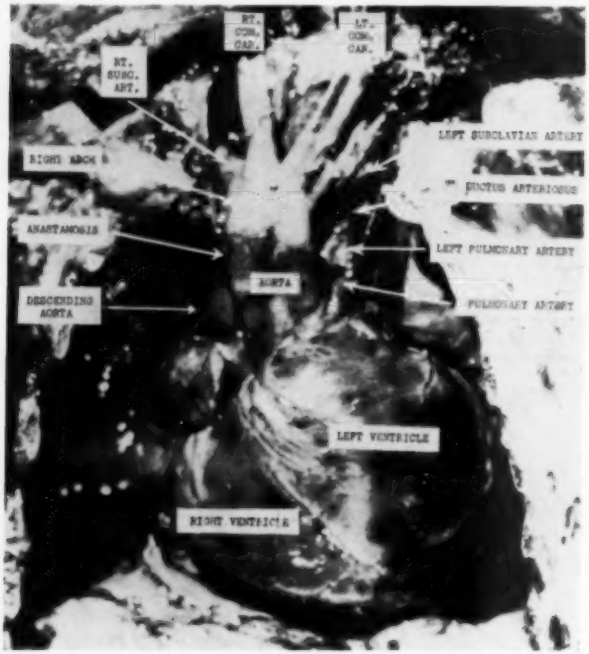

FIG. 5
Post-mortem photograph of heart in situ.

It was decided that the child's condition did not warrant further surgical manipulation. Consequently, the chest was closed; but as the skin was sutured the anaesthesiologist reported "cardiac arrest." The chest was re-entered and the heart massaged. A good, regular heart beat was obtained before re-closing the chest. Then, as the child was sent to the recovery room, all pulses disappeared again. Bronchoscopy was carried out and intracardiac stimulants administered, to no avail.

AUTOPSY

The autopsy report is quoted in part below:

"Left arm consists of bilobed stub protruding from left shoulder. Proximal lobe measures 1½ inches in long axis, and ½ inch in diameter. Attached to its distal end is a second lobe measuring ¾ inch long, ⅜ inch in diameter. At the end of the distal lobe is a well-formed nail. Right arm and lower extremities are normally developed.

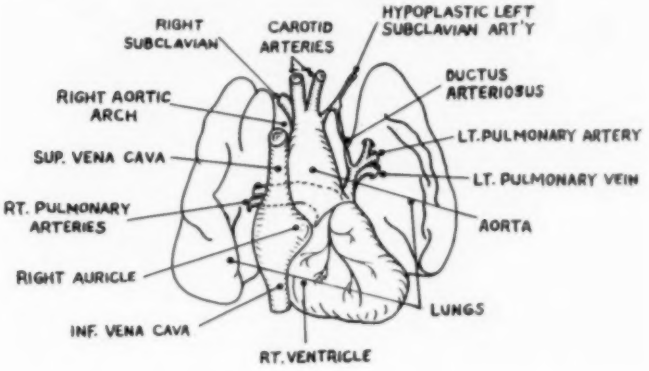

FIG. 6

Representation of character of cardiovascular abnormalities.

Two-thirds of heart consists of enlarged right ventricle, walls of which are 0.6 cm. thick. There is a septal defect through the membranous septum. There is moderate infundibular stenosis of the pulmonary valve. The base of the aorta over-rides this defect. The aorta arches to the right. Four large vessels arise from the arch, *the innominate being absent*. 2 cm. distal to its origin there is a small bulbous deformity in the wall of the left subclavian artery. This bulge is directed caudad, and from its apex, a small ductus arteriosus passes caudad for 1 cm., entering left pulmonary artery at a point distal to its origin. The left subclavian artery pursues its normal course to the left shoulder, but breaks up into numerous small branches immediately proximal to the previously described malformation of the left arm. The right and left vertebrals are considerably larger than expected." Of note, but not mentioned in the coroner's report, was the tiny caliber of the left subclavian in relation to that of the right artery. These can be compared in Figure 8. A & B. See also Figures 5, 6, 7.

EMBRYOLOGICAL CONSIDERATIONS

A. Right aortic arch occurs in approximately 20-25% of cases of the tetralogy of Fallot[4]. The aorta develops from three anlagen: the aortic sac, the fourth branchial arch, and the two dorsal aortae, which fuse together to lie to the left of the vertebral column. The

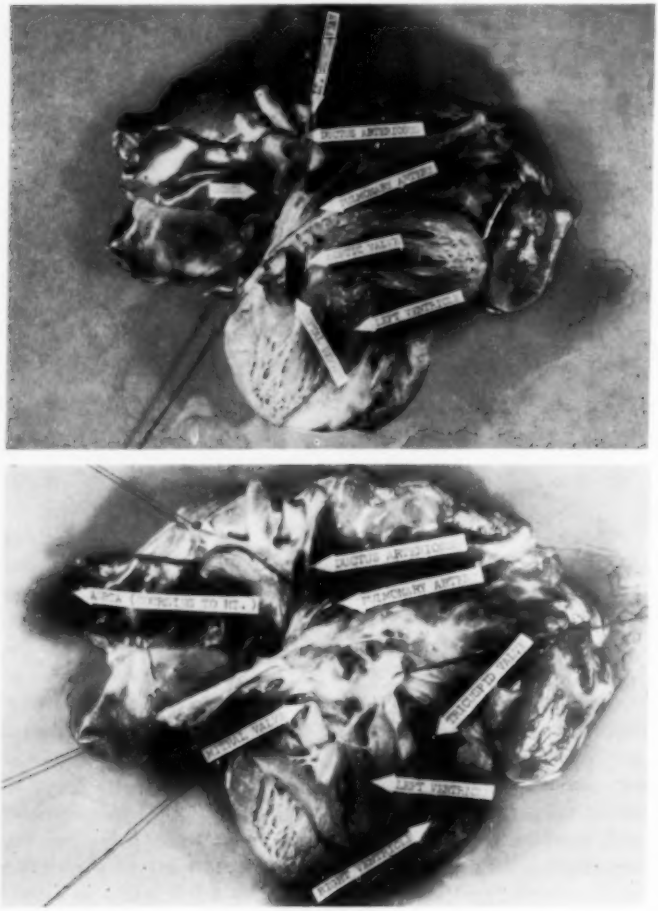

FIG. 7

A and B. The opened heart at autopsy. Note particularly the large interventricular septal defect, the tiny left subclavian artery, and the persistent ductus arteriosus connecting this vessel with the left pulmonary artery.

pulmonary artery and ductus arteriosus are derived from the sixth branch arch. Normally, it is the fourth left branchial arch which forms the arch of the aorta, and the fourth arch on the right which atrophies. Right aortic arch results from a reversal of this normal process, the fourth left branchial arch atrophies and the fourth right arch persists (see Fig. 8).

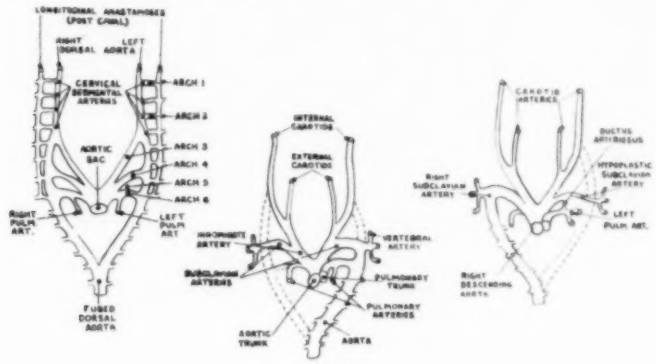

FIG. 8

Diagram of the branchial arch arteries to show: (a) derivation of branches of latter, and (b) suggested deviation from normal pattern which produced findings in this case.

In embryos of about 13 mm., the aortic sac, its left horn, and the left fourth arch artery form the arch of the definitive aorta. The right horn of the aortic sac enlongates to become the innominate artery. The proximal part of the left third artery becomes the left common carotid artery, and its distal portion forms the commencement of the left internal carotid artery. The innominate terminates by giving origin to the right third and fourth arch arteries. The former of these in turn becomes the right common carotid artery, and the commencement of the right internal carotid artery. The right fourth arch artery forms the stem of origin of the right subclavian artery. The left subclavian artery arises by the hypertrophy of a segmental branch of the left dorsal aorta, at or near the point at which the latter is joined by the fourth arch artery. This would lead to the conclusion that in the case presented, a failure of such hypertrophy to occur in the branch of the left aorta resulted in the diminutive vessel. Further, there was a failure of the aortic sac to elongate in the regular manner into the innominate, the subclavian and carotid vessels on the right originating rather directly from the third and fourth arch arteries.

B. As regards the underdeveloped left upper extremity, the best reference source at the moment is the comprehensive investigation of Birch-Jensen[6]. In this masterly discussion of congenital deformities of the upper extremities, the author has compiled records of practically every patient with an absence deformity of this type living in Denmark, born prior to 1947. He considers that such deformities may be grouped according to their etiology into exogenous or endogenous defects. Within the endogenous category, two essentially different types of anomaly develop; one resulting from a disturbance in the original hand plate before differentiation of the bone anlage, the other caused by a disturbance in the very bone anlage of the primordial hand. Such disturbances tend either in the positive direction, with development of supernumerary bones (polydactylism), or in the negative direction, wherein the rays are shortened and/or reduced in number.

Finding the usual terminology not sufficiently differentiated, Birch-Jensen set up the following classification for absence deformities of the upper extremities:

A. the endogenous groups
- I. (1) split hand
  - (2) atypical split hand
- II. ectrodactylism
- III. (1) radial defects
  - (2) ulnar defects
  - (3) radio-ulnar defects
- IV. (1) amputation of upper arm
  - (2) amputation of forearm
  - (3) amputation of hand
  - (4) symbrachydactyliasm

B. the exogenous groups
- I. (1) spontaneous amputation of upper arm
  - (2) spontaneous amputation of forearm
  - (3) spontaneous amputation of hand
  - (4) spontaneous amputation of fingers
- II. exogenous syndactylism

In accordance with this author's criteria, the case under discussion falls into the category of endogenous deformity: amputation of upper arm (IV (1) above). He states that such instances as this are characterized by the presence of rudimentary fingers, possibly a rudimentary hand: "a well-padded stump without scar formation or presence of bone is always indicative of amputation."

When it remains difficult to differentiate between the "amputations" of endogenous origin, and the "spontaneous amputations" of the exogenous groups, x-ray examination may decide the question by revealing congenital bone deformities in the former but not in the latter. It was noted that, in the case under discussion, two small bones were present in the rudimentary ray.

The etiological basis of these embryological abnormalities has been given a lot of thought by many investigators, but as yet there remain mostly surmise and theory. Among the factors which have continued to be put forward during the past three centuries are the following: amniotic complications, hydramnion or oligohydramnion and "other space-narrowing processes," umbilical cord slings, overturned uterus, "germ theory," psychic trauma, physical injury to mother, foetus, and the like. As may be seen, these are generally vague phrases which add little to our knowledge of how such growth defects actually occur. Of more concrete help has been this author's systematic classification of factors observed in his study:

1) the chance of getting a deformed child increases with increasing age of the mother. Father's age not a factor.

2) neither physical or psychic injuries to mother appeared to have any bearing upon the appearance of upper extremity deformities in the offspring.

3) there was a positive relationship between incidence of upper extremity deformity and length of interval between siblings in a family.

4) chance of having a child deformed in this way increases with increasing number of pregnancies.

In summary, Birch-Jensen observed that amputation of the upper arm is a very rare congenital deformity. For his definition of "rare" he provides the following: the incidence at birth is about 1 in 270,000, and the incidence in the population of his native Denmark he finds to be 1 in 450,000. He feels that this great difference is due to the fact that the "gene for amputation of the upper arm is a lethal factor for the foetus in a large number of cases." When present, congenital amputation of upper arm is frequently associated with like congenital deformities of the lower extremities. On the other hand, Birch-Jensen found that "apparently amputation of the upper arm is not associated with other malformations or diseases, at least not in the viable patients."

DISCUSSION

In considering the deformities encountered in this patient, and having studied these afore-mentioned publications, the possibility suggested itself that here may very well lie a cause-and-effect relationship. Arching of the aorta to the right in itself is not an uncommon finding at autopsy, as born out by the studies of Abbott and Taussig,[1,3] especially in association with the anomalies of the heart which go to make up the Fallot syndrome (vide supra). However, the four prime branchings of the aortic arch are most unusual, as is the hypoplasia of the left subclavian artery and the location of a ductus, coursing between this artery and the pulmonary vessel.

We have little explanation, actually, in light of present-day knowledge, for any of these intrinsic defects of the vascular system. But the finding of the hypoplastic left subclavian artery with this ductus strongly suggests the possibility that these vascular abnormalities may have had more that a casual relationship to the absence deformity of the left arm. Systole of the left ventricle normally ejects blood with force into the base of the aorta, whence it is thrown around the arch to the left and directed toward the origin of the left subclavian. In the case under discussion, on the other hand, several factors were at work to prevent any large volume of blood from entering this vessel which would offer the upper extremity its main supply. As blood was ejected from the left ventricle, the abnormal course of the aortic arch carried blood *away from* the developing ray. What blood did reach the mouth of the left subclavian was probably largely prevented entrance into that vessel by its small caliber. In addition, it would appear that the ductus arteriosus remained patent for a considerable period after birth, in which case a portion of the blood which did gain entrance into the subclavian in spite of these features, was promptly drained off again into the pulmonary circuit. Here indeed would be ample reason for the retarded state of growth of this extremity. It is an interesting conjecture.

CONCLUSION

Although a right arch associated with tetralogy of Fallot is not an uncommon circumstance, and the incidence of micromelia of an upper extremity has been found to occur 1:270,000 births, the association of the two has not been previously recorded in medical literature. Such a combination of abnormal development in a four

year old white male has been herein presented. Recording of this case was prompted not so much by this unusual association of anomalies as by the thought that explanation for the more physically apparent micromelia probably resided in the bizarre development of the great vessels in their origin from the base of the heart.

SUMMARY

1. The birth and development of a four year old white male is recorded, and his unusual combination of physical defects described. Following a surgical procedure, a complete revelation of congenital anomalies included the following:
   a) congenital cardiovascular disease:
      (1) tetralogy of Fallot
      (2) right aortic arch and right descending aorta
      (3) persistent ductus arteriosus
      (4) absence of innominate artery
      (5) hypogenesis of left subclavian artery
   b) micromelia, left upper extremity
   c) facial dysostosis
2. A review of the normal and abnormal embryological development of the cardiac, vascular, and extremity systems provides a probable relationship between the occurence of these anormalities.

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TUBERCULOSIS IN CHILDHOOD

Part V

V. HISTOLOGICAL OBSERVATIONS CONCERNING THE PRESENCE OF TUBERCLE BACILLI IN LYMPHONODOGENIC REGRESSIVE CHRONIC PNEUMONIA OF TUBERCULAR ORIGIN

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We distinguished two types of changes in investigating regressive pulmonary infiltrations in our human material: cases in which macrocellular intra-alveolar (rubber-eraser-like) condensations predominated (Group II), and others in which necroses (caseous pneumonia) prevailed (Group III). Tubercular lymph nodes discharging into the bronchial system were present in all instances considered here, in both groups, in a location excluding any doubt concerning the lymphonodogenic origin of the pulmonary involvements. As in our corresponding animal experiments, a lobar tendency of the aspiration-infiltration was apparent in almost every case. In the series of rubber-eraser-like infiltrations (Group II), we investigated two observations representing initial stages of chronic allergic aspiration-infiltrations (Case 1, A. 348/47, Case 2, A. 502/29). In both instances, intra-alveolar conglomerations of giant cells (large, multinuclear, syncytial elements) were disclosed, which corresponded in all aspects to occurrences of the proliferative stage of experimental superinfection infiltrates, developing during the first weeks after the second injection. Remarkably, in one of these cases (No. 1, A. 348/47) which was investigated appropriately, those giant cells—and all other cellular components of the inflammatory infiltrate—were laden with enormous masses of tubercle bacilli, just as in clinically comparable animals of our experimental series and in Bieling-Oelrichs' parallel investigations.

No doubt, we dealt here with the typical effect of an inflammatory fixation-phenomenon. Other cases of this group (Group II, Nos. 3, 4, 6, A. 237/47, A. 941/46, A. 829/49), displaying changes of the consolidation stage in its early or completely developed phase, were characterized by an absence of the agents, sparse examples of which could be detected only after persistent and intense search. Absence of tubercle bacilli was a predominant feature also in cases of the rubber-eraser-like pneumonia, in which the dis-

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integration and dissolution of the lymphonodogenic aspiration-infiltrations occurred (Group II, Nos. 9 and 10, A. 730/48, A. 617/45). Based on our experimental observations and on Bieling-Oelrichs' experiences, we arrive at the following conclusions: Directly after the discharge of softening tubercular lymph nodes into the bronchial system, an aspiration-infiltration develops, enclosing an excessive number of bacilli in its cells; soon, these agents disintegrate more and more, giving the aspiration-infiltration the aspect of an abacterial condensation.

We observed only one instance of a rubber-eraser-like pneumonia in which absolutely no necroses were present (A. 502-29 Frankfurt-M; Case 2 in Group II); we assume that the lymphonodogenic aspiration-infiltration in this case has not, as yet, accomplished its spread. In all other observations of this group, necroses were present, more or less extensively, inclined to delimitation, encapsulation and fibrous transformation. While necroses of the giant-cellular proliferative stage contained enormous masses of tubercle bacilli, necroses of later developmental stages of lymphonodogenic aspiration-infiltrations appeared to be increasingly free of germs. At any rate, it is true that tubercle bacilli may be present in excessive amounts in a predominantly cellular lymphonodogenic aspiration-infiltration, while—in other cases—necrotic areas of the condensations may appear almost sterile. These seemingly paradoxical combinations may appear even more surprising in lymphonodogenic aspiration-infiltrations in which caseous pneumonia predominates. In two cases (A. 598/47; A. 32/48, Cases No. 1 and 6 of Group III), representing the most acute stages of this series, necrotic territories, as well as cellular infiltrates, were permeated by excessive masses of tubercle bacilli—a feature which we consider to be the expression of an inflammatory fixation-phenomenon. Then, corresponding to the increasing intervals between lymphonodogenic discharge and death, the number of germs decreased progressively. In cases in which the discharge of tuberculous lymph nodes occurred more than three months before death, bacilli were almost nonexistent. Thus, we observed once more that the germ-content may appear independent from the morphological aspect of a lymphonodogenic aspiration-infiltration.

In the light of traditional concepts, the presence of considerable amounts of bacilli in cellular condensations may seem perhaps even more astonishing than their absence in necroses.

We assume it is of great importance that in these cases the germs are primarily located in large round cells ("macrophages") and

in their relatives, in syncytial giant cells, in elements which according to a widely-accepted opinion are to be considered as the source of immune bodies. Captured ("fixed") and inhibited in their virulence, that is, in their phlogogenic properties, the germs face their eventual destruction. Our observations indicate that the massive disintegration of the bacilli proceeds approximately during a five-week period after the occurrence of the lymphonodular discharge.

In respect to the cleansing of the aspiration-infiltrations, we made the following observations: The elimination of the inflammatory products may proceed by their dissolution, without damaging the pre-existent pulmonary structure to a significant degree. Or we may observe extensive disintegration of the condensed territory, cavitation, indicating parenchymal losses during the healing process. A third type of regression in our series was characterized by the diffuse cicatricial devastation of the involved pulmonary tissue. No doubt, these three forms of healing of allergic aspiration-infiltrations may occur parallelly, in one and the same case.

While the dissolution of intra-alveolar cellular conglomerations and the healing of chronic pneumonic processes by cicatricial devastation accord with the general concepts in respect to the reversibility of a pulmonary condition, the healing by intermediary cavitation needs particular consideration. Two instances (A. 10/47 and A. 7/52, No. 1 and 2 in Group I) of our material investigated here permit the statement that even very extensive disintegration not only does not impede the reversibility of an allergic aspiration-infiltration, but, on the contrary, may turn out to be very beneficial. Also, observations of this type may dispel doubts concerning the assumption that extensive caseous-pneumonic aspiration-infiltrations, like those listed in Group III, can be considered to be of regressive nature.

In pre-infected animals, the rapid disintegration and dissolution of caseous aspiration-infiltrations occurred 6-8 weeks after the intratracheal superinfection. In massive and cavitated aspiration-infiltrations of comparable age, listed in groups II and III, almost no tubercle bacilli could be detected. Therefore, we believe that the extensive necrosis of an allergic macrocellular lymphonodogenic aspiration-infiltration, as well as its dissolution, results more or less independently of the presence of germs, simply from an instantly-occurring permanent interruption of the blood circulation, which already was markedly retarded within the condensed pulmonary territory.

VI. COMMENT

Pathologic-anatomical observations, as presented in the foregoing, show with very great clarity that chronic pulmonary condensations accompanying tuberculosis, which prove to be reversible in clinical radiological examinations, that is, capable of healing and cicatrization, result, in general, from inflammatory processes. We observed that both chronic pneumonic infiltrations characterized by the absence of necroses, and extensively necrotic tubercular structures, may be eliminated without trace. It is only a question of time whether an infiltrate, which initially displayed massive necroses, becomes transformed into large tuberculous scars, or develops to a stage in which only nonspecific, devastated sclerotic areas remain; if the patient survives the initial disease long enough, the last of the sequelae may completely vanish. Hand in hand with the disappearance of pulmonary structures, which, as a consequence of the involvement were prohibited from functioning, a substitution and compensation by the neighboring tissues occurs: a process, characterized by the endeavor to reconstruct the original shape of the organ. Thus, we understand that the results, which were considered products of reversibility, depended on two factors: 1. The inherent healing ability of infiltrations and defects, induced in the initial period of pulmonary tuberculosis by the lymphonodo-bronchogenic superinfection, and 2. The ability of the organism to reconstruct its parts deformed by disease. However, it would be illusory to insist on an integral restitution without considering that in condensed areas, even if the infiltrate shows a purely cellular composition, pulmonary parenchyma always suffers losses. On the other hand, our observations revealed clearly that the cavitation following the dissolution of infiltrates—even if it sometimes may become dangerous—in many cases accelerates the definitive liquidation of the consequences of lymphonodo-bronchogenic superinfection, and facilitates the compensation by adaption of the neighboring tissues.

Time is the most important factor in the regression of benign pulmonary involvements. The greater the number of years elapsed after the onset of a lymphonodo-bronchogenic aspiration-infiltration, the nearer normal becomes the condition of the lungs. It is indeed possible that even very extensive pulmonary lesions, due to lymphonodo-bronchogenic aspiration, may heal without leaving any traces, in 30 to 40 years. Therefore, perfectly normal-appearing lungs of elderly persons may have sustained considerable damage in earlier periods of life.

Pulmonary collapse regularly accompanies inflammatory pulmonary condensations which are capable of healing. In small infiltrations of this type, there are always present collapsed alveoli and acini, while in areas of large condensations, the collapse of entire lobuli may occur. These changes, although only indirect consequences of the inflammatory processes, have the same fate as the primary disease: if the inflammatory condensation can be reabsorbed without intense structural pulmonary changes, then, sooner or later, the collapsed pulmonary parts will also function normally; however, in cases where infiltrated areas are subjected to destruction, the included collapsed pulmonary tissue—even if entire lobuli are involved—will also be doomed. This fate may overcome whole pulmonary lobes, which, following spontaneous pneumothorax, or, consequent to bronchial occlusion, forfeited their air-content and were unable to reopen at the appropriate time. However, even in instances of those reversible condensations in which the radiological symptoms were in fact induced by genuine pulmonary collapse, the radiologic clarification of the involved pulmonary parts often is caused not by resuming respiration, but by a progressive cicatricial contraction of the devastated atelectatic tissue.

These statements express our opinion also on Rössle's conclusions: *"Epituberculosis" is an inflammatory infiltrative process, which, in its function as a cause of radiological condensation, may be enlarged and enforced by pulmonary collapse.*

Thus, we return to the unbiased evaluation of processes causing pulmonary condensation in phthisis, which was held in acceptance before Rössle's publication: It is possible that in clinical, and even in pathologic-anatomical considerations, inflammatory infiltrations, which appear as a consequence of bacillary spread, may be confounded with other condensations—with hemorrhagic infarction, simple pulmonary hemorrhages, collapse—however, it is the task of every investigator to discriminate between these basically different types of pulmonary lesions and to define a hemorrhage as a hemorrhage, collapse as collapse, and not as "epituberculosis"!

Now, to close the chapter on epituberculosis, we propose to drop this inaccurate concept of a disease, together with its vague nomenclature. There are no "epi" tuberculous condensations of the pulmonary tissue, but only manifold inflammatory infiltrations developing under the direct influence of tubercle bacilli, or their products and compounds. The appearance of these pulmonary changes is to the same degree characteristic of tubercle bacilli as are—in spite

of great differences in their morphologic aspects—gummas, white pneumonia, or diffuse interstitial hepatitis for the spirochaeta pallida.

Indeed, the disease which for many years was known as "epituberculosis" differs from other characteristic changes of chronic phthisis because the conditions which induce its appearance are extraordinary: Shortly after the onset of a tuberculous pulmonary involvement—caused either by exogenous infection or by reactivation of old foci—enlarged and necrotic parapulmonary lymph nodes discharge into the bronchial system, inundating, with their bacilli and specific phlogogenic substances, large pulmonary areas at a moment in which the sensitivity of the pulmonary tissue has reached its highest degree, and immunity already is forcefully effective. As a consequence of this peculiar combination of favorable and unfavorable influences, very extensive, however benign, inflammatory condensations develop, which, if the organism survives long enough, heal, or may even disappear without leaving a trace.

Thus, we are confronted by a pathogenetically, morphologically and clinically particular morbid entity, characterizing a certain period of the beginning pulmonary tuberculosis and caused by the discharge of necrotic lymph nodes into the bronchial system. We propose to term this type of pulmonary infiltration a benign, tuberculous, lymphonodo-bronchogenic segmental, or lobar infiltration.

The course and healing of lymphonodogenic rubber-eraser-like pneumonia is often accompanied by bronchitis or by diffuse and sacciform bronchial dilation. We assume that these conditions later, after the complete extinction of the tubercular inflammation, may help infections to establish a foothold, thus promoting the development of a post-tubercular "middle-lobe syndrome" or of a chronic bronchiectatic disease.

SUMMARY

1. Regressive pulmonary condensations in the course of tubercular conditions, in general, represent chronic pneumonic processes, caused by the discharge of softened, caseous lymph nodes into the bronchial system. We deal in these cases with aspiration-infiltrations, often evidencing lobar extension or lobar tendency; at any rate, their segmental character always is conspicuous.
2. Regressive pulmonary infiltrations frequently occur in children, as well as in adults, in the initial period of fresh primary

tuberculosis, or in the course of chronic processes, following new lymphonodo-bronchogenic episodes.

3. Two types of regressive pulmonary infiltrations are to be discriminated:
   (a) Chronic pneumonic condensations, macroscopically characterized by rubber-eraser-like consistency, and microscopically by macrocellular intra-alveolar infiltrations, in which necroses are rather inconspicuous.
   (b) Predominantly caseous-pneumonic processes, representing the result of particularly abundant discharges of voluminous necrotic lymph nodes.
4. Three stages may be differentiated morphologically in the development of regressive pulmonary infiltrates:
   (a) a short proliferative phase, in which intra-alveolar, syncytial giant cells predominate;
   (b) the stage of consolidation, in which the intra-alveolar infiltrate is primarily composed of mononuclear alveolar histiocytes; and
   (c) a long period of cleansing and healing.
5. Both rubber-eraser-like and caseous-pneumonic regressive condensations may be accompanied by extensive cavitation. Disintegration and dissolution of the infiltrated pulmonary tissue signify, in general, the acceleration of the cleansing and healing process.
6. The initial stage of a lymphonodogenic regressive aspiration-infiltration is characterized by large amounts of tubercle bacilli in cells and necrotic areas of the condensation, indicating the occurrence of an inflammatory fixation-phenomenon.
7. While the rapid development and lobar extension of lymphonodogenic, regressive infiltrations reflect an increased inflammatory susceptibility, the disappearance of histologically detectible germs signifies the effect of a vigorous postinfectious immunity.
8. There exists no regressive pulmonary process of tubercular origin, occurring without any parenchymal destruction. The seemingly ideal restitution of clinical-radiological condensations accompanying pulmonary tuberculosis, which perhaps persisted for many years, may be simulated by progressive, diffuse devastation, or by the collapse and cicatricial shrinking of pulmonary lobes, severely affected by lymphonodogenic involvements.

9. The healing of regressive lymphonodogenic aspiration-infiltrates very frequently is accompanied by diffuse or sacciform bronchial dilations. Later-occurring nonspecific infections may then induce the appearance of a chronic bronchiectatic disease.
10. Regressive, inflammatory pulmonary condensations, displaying all morphological, bacteriological and allergic qualities of spontaneous diseases in human pathology, may be produced in rabbits, appropriately pre- and superinfected.
11. Atelectatic pulmonary collapse, accompanying intrathoracic lymph-node tuberculosis in various extensions, has to be essentially discriminated from regressive lymphonodogenic aspiration-infiltrations.
12. There is no regressive inflammatory pulmonary condensation in the course of a tubercular disease, developed independently of tubercle bacilli. Therefore, the concept of an "epituberculosis", as defined 25 years ago and still widely accepted, remains without foundation. Also, it seems misleading to employ this term in the future for cases in which, following intrathoracic lymph-node tuberculosis, the collapse of pulmonary parts occurs. The designation "lymphonodogenic atelectasis" appears to be more correct. Indeed, the fact should always be remembered that "pure" atelectasis by lymphonodogenic compression is an exceptional phenomenon in tuberculosis, while aspiration-infiltrates predominate.

Addendum:

In a paper, "Segmental Atelectasis in Children with Primary Tuberculosis," published in the May 1959 issue of the American Review of Tuberculosis (Vol. 79, No. 5, p. 597-605), S. Frostad, Oslo, Norway, reported results of bronchoscopic examinations in a series of 90 children suffering from segmental atelectasis following primary tuberculosis. The author identified segmental atelectasis in children with epituberculosis. "Simon and Redeker . . . called it perifocal inflammation, but Rössle, in 1936, showed that epituberculosis in reality was atelectasis from compression of a bronchus by lymph nodes. He distinguished the pure atelectasis from the complicated cases which often show pneumonic foci as a result of aspiration of bacillary material discharged from the perforated lymph node. The adjacent lymph node presses the bronchus and closes the corresponding bronchial segments, which results in a pure atelectasis." Frostad endorses Rössle's assumptions. How-

ever, it seems that he does not know at all the publications of the present author concerning lymphonodogenous bronchial lesions in tuberculosis; also, he failed to mention corresponding publications of Lewenfisz and Margolisowa (1949), Simon (1951), Rietschel (1952), Erichson (1953), Brügger (1955), and Laft, Goldberg and Russel (1956). Some of these authors—and many others of the last few years—emphasized the tubercular inflammatory nature of "epituberculosis" and the paramount importance of lymphonodogenous perforative bronchial lesions in its pathogenesis. In spite of these omissions, Frostad's paper is of great value, as the author observed bronchial stenosis due to tubercular lymph node involvements in 67.8 per cent of his cases. Discharge of tuberculous lymph nodes into the bronchial system was present in a further 27.8 per cent. "In only one child were the findings completely negative at bronchoscopic examination." Bronchographic examination in 33 children disclosed abnormal bronchograms in 27. Frostad's observations prove that clinical investigations can reveal exactly the same frequency of lymphonodogenic bronchial lesions as did the anatomic examinations of the present author.

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A SIMPLE METHOD TO ASSURE PROPER PEDIATRIC EAR EXAMINATIONS

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More than one in every three ears examined, in which pathology is present, may have complete obstruction of the tympanic membrane by cerumen. Involvement of the middle ear makes up a large portion of pediatric pathology and appears in some degree in practically all acute respiratory infections in infants and younger children.[1] Pediatricians have always been plagued by the problem of visualizing cerumen-occluded tympanic membranes in recalcitrant patients. Blunt curretage, peroxide or oil instillations, have only limited success and are difficult, time consuming, and indeed, may be dangerous.

We have for some time been using a cerumenolytic material† for clearing the ear canal of occluding waxy material, with a high degree of success. The preparation can be used either by instillation into the ear, followed by swabbing or gentle irrigation of the ear canal about twenty minutes later, or by instillation, allowing the material to remain in the canal overnight, and then gently irrigating the next morning. We have previously reported 75% success with the immediate method and 95% with the overnight method using one treatment only.[2] With repeated treatments, it is possible to achieve 100% results.

From a practical point of view, the procedure of instillation, the waiting of twenty minutes, and irrigation does not lend itself well to office space and facilities. Ideally, removal of wax should be accomplished before the child is brought to the office for examination. Thus, proper visualization of tympanic membranes is assured without an expenditure of office time and space.

Since all of the procedures involved in removing occluded ear wax using Cerumenex and gentle irrigation are simple and safe, we decided to determine whether they could be carried out efficiently at home by the parent prior to examination.

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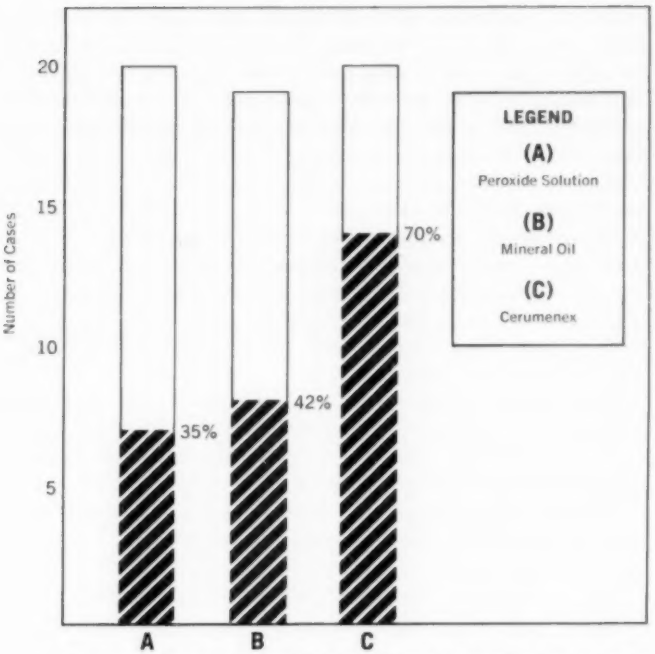
† *Cerumenex ®, Distributed by the Purdue Frederick Company, New York, N. Y.*



Note: Total number of patients treated indicated by height of bar (In bar B one case would not permit therapy). Shaded area indicates number and percentage of cases in which successful results were obtained.

METHOD

A group of sixty children with at least one completely cerumen-occluded ear canal was formed by selections of children presenting themselves for pediatric examinations in the pediatric clinic and in office practice. This group was selected without regard to other disorders eliminating only those children who were sufficiently acutely ill to preclude their return for a follow-up examination the next day. In this same random manner, they were assigned to three groups of twenty children each. The only deviations in this method of selection were in cases where, because of language difficulty or other inability to achieve understanding by the parent, we felt that the procedures would not be carried out properly. Instructions were given to the parents to fill the ear canal half-full with the testing material, with the child lying on its side, to plug the opening with a cotton plug that

night and to syringe out the ear canal with warm water the following morning. For this purpose, they were given a dropper bottle of liquid test material and a two ounce Davol rubber ball and nozzle type syringe. They were instructed to fill this completely full with water just warm to the touch when tested on the skin of the inside of the wrist, much as the milk in an infant's bottle is tested. Irrigation was to be done with only sufficient pressure to force the water out of the syringe, with the opening of the nozzle just at the entrance of the external canal, and always actually in view. The child was placed on its side on a towel with the ear being treated facing up and the irrigation was carried out essentially only by gravity, rather than by pressure. They were then to bring the child in to have the ear canals and tympanic membrane examined.

Each group of twenty children was tested with a different cerumenolytic material, the three materials used being Cerumenex, hydrogen peroxide (this was the ordinary household antiseptic type of 3% solution), and mineral oil.

Otologic examinations were carried out before and after treatment to evaluate the degree of cerumenolysis.

RESULTS

The children varied in age from three to twelve years with all races, white, colored and Chinese being included. Three of the 60 children complained of moderate to severe pain in the ear when they first presented themselves, and one of these would not permit the procedure to be carried out by the parent. The other two were subsequently shown to have an acute catarrhal otitis media. All the other parents reported no difficulty in carrying out the instillation or the irrigation, and when the wax was successfully removed, could clearly see it in the wash water which drained from the ear. One child of the sixty children developed an itching erythematous eruption of the external auditory meatus and surrounding area of the pinna of the ear. This subsided in forty-eight hours without therapy.

The results are summarized graphically in Figure 1:

DISCUSSION

In the hands of parents, the procedure of placing a cerumenolytic in the ear canal, allowing it to remain overnight, and then gently irrigating the ear canal, was somewhat less successful than

in our own hands. Only 70% of the ears were cleared with the use of Cerumenex in this study while we had been able to clear 95% by this technique when we carried out the syringing ourselves. However, the study clearly demonstrates the great effectiveness of Cerumenex, even in untrained hands, as a cerumenolytic over two other materials which have been in use for many years. Also, the most important of all, this study demonstrates that a simple technique can be safely and effectively carried out by parents prior to examinations of the ear canal, so that adequate examination and prompt therapy can be assured.

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LEIBMAN, J. AND NADAS, A. S.: *Heart Disease in the Newborn.* (Pediatric Clinics North America. Nov. 1958, 1087).

The physical examination, particularly the identification of congestive failure and the recognition of cyanosis, probably provides the best evidence of heart disease in the new born period. Murmurs, although of themselves of dubious significance, are most likely to indicate heart disease at this age than at any other period.

The electrocardiograms and the radiograms are only ancillary tools in the diagnosis. Fluoroscopy should be used sparingly because of the increased amount of radiation involved.

Recognition and vigorous treatment of congestive failure or anoxia are more important than arriving at the correct diagnosis at this age. Only very rarely is treatment in the newborn dependent upon diagnosis. Surgical intervention today is only exceptionally indicated in cases of extreme pulmonic stenosis, tricuspid atresia, coarctation of the aorta or patent ductus arteriosus.

Since most anatomic diagnosis at this age are based upon probability rather than anatomic signs and symptoms, it is rarely wise to be too specific about prognosis for some weeks after the discovery of heart disease.

With the further advances in cardiac surgery, accurate anatomic diagnosis may become of paramount importance even in the newborn period. Under these circumstances, all the clinical and physiologic diagnostic tools will be utilized.

AUTHOR'S SUMMARY

Pediatric Conference

THE ROOSEVELT HOSPITAL, NEW YORK

February 18, 1959

Edmund N. Joyner III, M.D., Chief of Pediatrics, presiding

CONRAD M. RILEY, M.D., Associate Attending Pediatrician, Babies Hospital, N.Y., Associate Professor of Pediatrics, Columbia University, N.Y., Guest

DR. JOYNER: I think we'll now get started. We're very fortunate in having Dr. Conrad Riley, Associate Professor of Pediatrics at Babies Hospital with us today, and our cases illustrate various forms of the more common diseases of the kidneys. We'll start with a very short presentation of those and then turn the floor over to Dr. Riley.

RESIDENT: The first case is an 8 year old boy who came in with the chief complaint of brown urine and puffy eyes. The child was well up to 10 days prior to admission when he developed a slight cold, fever, malaise, and swollen glands in the neck.

On admission, physical examination revealed a rather sick-looking child with a temperature of 101, pulse 160, respiration 20. The blood pressure was 100/70. His weight was 63½ pounds. His face was puffy. Ears, nose, throat were negative. The neck revealed mild cervical lymphadenopathy, and there was a grade II systolic murmur. Liver was two fingers below the right costal margin.

Laboratory data: CBC was normal, ESR was 21, BUN 27.4, urine was slightly acid with many red and white cells.

He was placed on penicillin, bed rest, and during the first two days, his urine output was very low, but then increased. He did well. His BUN went down to 21. In one week he lost 4½ pounds, and urinalysis showed no albumin, only a few red and 21 white cells.

The second case is a 7 year old boy who came in with generalized convulsions and a 3-day history of cold, fever and joint pain. To control the convulsions, amytal was necessary.

Physical examination revealed a child in a post-convulsive state; the temperature was 100, the pulse 60, respiration 40, blood pressure 110/60. There was a slight edema of his face, a systolic

murmur, a liver two fingers below the right costal margin, and pitting edema of the lower extremities.

Two hours after admission, blood pressure rose to 160/135 and remained high for the first week in the hospital, but was controlled with magnesium sulphate and phenobarbital. His urinalysis on admission showed one-plus albumin, a few red cells, and a few white cells. He did well the first week on penicillin and bed rest, and because of the convulsions, a spinal tap was done which was negative. An EEG revealed a focus in the right occipital area. His urine became negative and his blood pressure normal.

DR. JOYNER: We will now hear another presentation.

RESIDENT: The third patient was S.J. who came in with a one-month history of puffy lids in the morning. She also had swollen ankles for four days prior to admission and ran some fever. On admission, she was noted to be febrile, her lids were puffy and she had pitting edema of the feet and lower extremities. Her blood pressure was 90/60. She had a tachycardia and the only other positive physical finding was diminished breath sounds at both apices. Her hemoglobin was 10 grams. W.B.C. was 15,000. She had +4 albuminuria. She had 15-20 white cells in her urine, no red cells. On x-ray she did have a pneumonia. CRP was negative and ESR was 12. The total protein was 3.4 grams with an A/G ratio which was reversed, 1 gram of albumin to 2.4 of globulin, and she had an elevated cholesterol with a total lipid of 2,000 milligrams percent.

She was placed on steroids and penicillin and about the 9th or 10th day she diuresed and she lost about 6 lbs. Her protein came up, her albumin especially,

Her urine cleared up about that time and the steroids were tapered off. She was on steroids for a total of about 3½ weeks. Her pneumonia cleared up very nicely under penicillin, and she had a very benign course and has done very well since then.

Another patient is a 13 year old boy who came in with a 3-day history of swollen lids. On examination he was noted to have puffy lids and slightly swollen feet. His blood pressure was normal on admission and hemoglobin was 13 grams, white count unremarkable. He had an elevated ESR of 36.

On admission his BUN was 16 milligrams percent with a low total protein and a reversed A/G ratio. The total protein was 4.2, albumin 1.9 and globulin 2.3. He had 4-plus albumin in the urine. He was placed on bed rest only and treated for the albuminuria. Because of a positive tuberculin, he was also on isoniazid. About 10 days later, steroids were started. He lost about 14 pounds and his urine began clearing. After his urine

was clear, we tapered the steroids off, and he started with albuminuria again, so we put him back for a second time on the steroids; this sequence has recurred.

We have had him three times on steroids. Each time steroids were withdrawn, he has had albuminuria again. He had a transient period during which his BUN went up and after the diuresis, it came down again to normal limits. The highest was 51 milligrams percent and his cholesterol had gone up to as high as 470 milligrams.

DR. JOYNER: I think we will proceed with Dr. Riley. As I said before, these were illustrative cases. We considered the first two nephritis; the third as nephrosis, and the last, a mixed form of Bright's Disease.

DR. RILEY: I gather from the cases you've selected that you're about as puzzled as everyone else is in classifying these varieties of what, for general purposes, we call Bright's Disease, so I thought I might spend a moment talking about how I've resolved this problem in my own mind.

Secondly, I think the place where there's been the most change from the management point of view, is in the problem of nephrosis, so I thought I might wind up by talking about the way we are managing it in our hospital. There are some interesting features of these cases that have been presented here.

The first case was one of a fairly typical acute nephritis. There was no significant blood pressure elevation, and there was something that I think people aren't always accustomed to thinking of—a fair degree of pyuria. There was described here a urine with 25 to 30 red blood cells per high power field, and loaded with white cells. I think oftentimes when a child comes in, especially with the red herring that I note was thrown into the physical examination, of tenderness in the costo-vertebral angles, and you find a moderate amount of pus in the urine, it's a little hard to be sure whether this is an acute exogenous infection, such as pyelonephritis, or whether this is an acute glomerulonephritis.

I think what would clinch the matter for me in this first case is the fact that the child did lose from 63½ pounds on admission, to 57½ pounds on discharge. We can say with considerable sureness that edema is not associated with pyelonephritis; therefore any question that we may have had about the pyuria representing acute infection initially, would be put aside in my own mind by the fact that the child lost the edema during the course of his hospital stay.

In the second case, it is interesting that the boy was admitted to the hospital in convulsions, and yet, the first blood pressure

recorded on admission was 100/60, which is certainly not very high. One wonders if he could have had a hypertension prior to the beginning of his convulsions, which came down with the convulsive episode and then which gradually rose again while under observation in the hospital. Other than that, he would seem to be a reasonably good acute nephritis, who cleared fairly rapidly under treatment.

I think I might say one word there. I've been awfully impressed in the few times I've had the opportunity to use it at how effective a hypotensive agent intra-muscular reserpine is in these cases of acute nephritis. When the blood pressure begins to climb and you begin to get worried about it from the point of view of the development of hypertensive encephalopathy, this is a more innocuous way of controlling it, to my mind, than magnesium sulfate. I'm concerned in my own mind about the dangers of magnesium intoxication. But apparently you can give very large doses of reserpine intra-muscularly, safely and with good effect. It has been very useful in bringing blood pressure down within a half-hour to an hour—to a much more comfortable level for the doctor. I don't know whether it makes much difference to the patient, but at least the doctor rests more easily.

The discussion of the use of serpasil was given by Etteldorf and others, in "The Journal of Pediatrics" in February 1956. If you're not familiar with that paper, I think you'd find it awfully useful in handling your acute nephritics with hypertension.

Then, there are the other two cases that are more characteristically nephrotic, as shown by their hypoproteinemia, with the first little girl showing a very marked and nice response to steroids, and no relapse so far. I would have my fingers crossed as to her future.

As to the ages at the time of onset of nephrosis, we collected some 600-700 cases from various parts of the country; the peak incidence is between 18 months and 4 years of age, but recently, we have been seeing more young adults with this disorder. I don't think this is too specifically a childhood disease, although it certainly is more common in the early years. I would not hesitate to make a diagnosis of this same type of idiopathic nephrosis in a 13-year old, a 15-year old, or a 20-year old, or perhaps even a 30-year old or 40-year old—but that's getting a little far removed from my usual experience. Now I think I'll move into the discussion of classification.

There has been a great deal of battle down the years among people with various interests—internists vs. pediatricians—people especially interested in kidney disease vs. people without such

specialization—as to how well these various types of Bright's disease fit together. I think one great disservice which is done to the embryo doctor is trying to make this thing look too simple. As I went through medical school, I was given to believe that chronic nephritis was one thing—and a very definite thing—and frequently had a nephrotic phase to it. Also "pure nephrosis" was something else entirely and completely unrelated to the nephrotic phase of chronic nephritis. Acute nephritis was something else again, and everything seemed very simple. There was a nice little cubbyhole for everything, and everything *should* fit into its own cubbyhole!

Once you begin to see patients, however, you realize that though in their typical forms these cases really do fit, there are a great many which do not represent anything typical. To put them anywhere with any degree of satisfaction, you have to have a fairly elastic group of cubbyholes. They should have tenuous walls rather than discrete borders.

It is our feeling that there are two conditions, from a strictly clinical point of view which often run true to type. A great deal of the pathological picture that has been presented through the years, obviously has been based on autopsy work. It is not fair to assume that what you see at the time of death, represents how the tissue got in that condition in the first place. It seems that we are now undergoing a period of changing thoughts on morphology, which will be broadened as people do more and more renal biopsies, and they see how a picture evolves instead of looking at it after it's finished. So, I think it's too early to talk about it then from a morphological point of view, and I would like to adhere strictly to this clinical point of view. With this as background, let us turn to two clear-cut entities. There is acute glomerulonephritis as represented by the first patient, which is a self-limited benign disease in most instances, and does not lead often to any particular complications.

At the other end of the spectrum is what I have labelled "primary nephrosis." I think "cryptogenic" or "idiopathic" would, however, be more suitable terminology because as we learn more, we will probably find new causes for the syndrome; so some of what now falls into the primary group, may well be transferred to the secondary category.

In between those two nice mountain peaks of security, there's a "slough of despond" to quote from Bunyan . . . perhaps it would be better to call it a "slough of agnosticism". . . where we don't really know what's going on. I don't think "lipoid" nephrosis is a good term because all types of nephrotic syndrome have

lipemia, lipoid bodies in the urine, lipoid droplets demonstrable in the tubules after death, etc., so let's talk simply about the nephrotic syndrome, or as I frequently do, just simply nephrosis. I'm sure in many instances it's secondary to something else that we do not know about.

In adults, it's frequently seen as part of lupus erythematosus, and I've seen one child as young as 5 years of age with nephrotic syndrome on this basis, but it's rare in children.

I think it is safe to say the Kimmelstiel-Wilson syndrome won't be seen in childhood because I think this is something where with diabetes, it has to be of long standing before you begin to get these secondary changes of nephrotic syndrome.

We've seen drug nephrosis in childhood, and I think probably the most common cause of this is tridione—of which we've had two or three cases. Other possible causes should be mentioned, such as amyloidosis, renal vein thrombosis, and you can continue for quite a while on various things that are said to have produced it from time to time. The most recent entry in this field is sickle-cell anemia, reported by Dr. Shreiner in Washington. So the nephrotic syndrome then, can be secondary to a great many things seen rarely in childhood.

Once in a while you see an acute nephritis which immediately goes into a nephrotic syndrome. I don't know where such a case belongs. Maybe it doesn't belong under the term "acute nephritis" at all. Patients with such a picture, in my experience, have had a rapid downhill course. Fortunately there have been only a few. They start off with acute hematuria, hypertension, and they begin to swell, and the first serum protein you get is already beginning to show dropping of the albumin, so that the situation develops very rapidly.

It is common belief that chronic nephritis ordinarily arises from acute glomerulonephritis. On the other hand, the number of instances where this is a demonstrated fact are very few and far between. Everybody assumes that because it is known that acute nephritis can exist in a sub-clinical form—Rammelkamp demonstrated this quite satisfactorily—everybody who has chronic nephritis must some time or other have had an unrecognized acute nephritis.

Now this is the sort of argument that I can't disprove; contrarywise, the person who proposes it can't prove it either, and I think it's just as fair an argument the other way around—that chronic nephritis is in itself a disease and not necessarily an outgrowth of acute nephritis.

On the other hand, there are a few instances where we have actually seen what *looks* like an acute attack of nephritis go into a chronic nephritis, so I believe that is a possible pathway.

Similarly, the nephrotic syndrome is thought, or was thought by writers of adult textbooks, usually to be a by-product of nephritis and we have seen cases where there has been this progression of events. Perhaps it would start with an acute, go to a chronic, and go on to a nephrotic syndrome; but again, this is a rarely observed phenomenon. A common assumption is that the nephrotic syndrome, secondary to chronic glomerulonephritis, is a much more common thing than the primary or idiopathic nephrosis. I don't believe it. I think it must be very rare in children. The usual age of onset makes it unlikely. Even in adult records, you have a hard time finding specific examples of this, although we do find a few, but I certainly don't believe they're the regular thing.

On the other hand, I do think that the secondary nephrotic syndrome from whatever cause, often gives rise to chronic destruction of the kidney, as the idiopathic nephrotic syndrome gives rise to chronic destruction of the kidney. Now what does chronic nephritis come from? Well, I think in a good many instances it is idiopathic. That's always an easy way out. I know in some instances that it results from anaphylactoid purpura. What has interested me very much are the familial cases. I know of maybe half a dozen different families whose child is brought in with the urinary findings of chronic nephritis, where there's a large group of uncles, aunts, cousins, etc., who have had something called Bright's disease, many of whom have died in their 30's. It's not a disease with a necessarily benign prognosis, and I've been picking these children up under ten years of age, with nothing to show except hematuria and proteinuria.

I suspect this is probably a different kettle of fish from other varieties of this because in most instances, chronic nephritis does not tend to repeat in the family tree. It seems that when you do find more than one case in the family, you find quite a few cases, which is a surprising thing.

Now what about prognosis in nephrosis?

In another cooperative study, we took patients who had their onset between 1946 and 1950 when the availability of steroids and ACTH was so slight that these patients, if they received steroid treatment at all, could not have received it early in the course of their disease. We compared this survival curve with those with onset in 1952-1957 when it is very likely that they received steroids and probably received them in a fairly regular fashion.

Certainly the intensity of steroid administration has been increasing steadily between 1952 and 1957, and I have a strong suspicion that a four-year follow-up on the ones started in let's say 1956, will show even better results.

Well, the difference of survival in the group after four years from the beginning is something around 75% among the recent group versus 60% for the earlier. Statistical tests on this show a high degree of probability that this is not something due to chance alone.

You can question if it is due to better chemotherapy? Is it due to closer attention to your patients? I can't prove that it isn't due to these other things, but there are a good many indications to suggest that it is due to steroids. Some of those that come to my mind are the fact that when you treat with steroids you not only get rid of edema, but you also get rid of proteinuria, the serum protein returns to normal, and everything clears up. So I think it's fair to assume that this difference is due to steroids themselves.

In a much smaller group of our own patients, we have tried to evaluate the condition of the survivors. Now, four years after onset, we divided the individuals up as to what their present status is.

Not only do we have a smaller proportion that have gone into irreversible renal damage, but we have a larger fraction that have gone on to something that might be called cure—I'd be awfully cautious about using this word "cure" because we certainly did see in the old days patients who went into a complete remission and then several years later would relapse. I think the number of such patients we're seeing now with the present steroid treatment are increasing. Contrary-wise, it is reassuring to realize that when they do relapse, they seem again to respond to treatment very well, so it may be that with continual or intermittent or repeated treatment, they can be kept going for a normal life span. This is somewhat wishful thinking as we haven't the evidence to prove it.

So much for the background of why I think steroid therapy is something worth doing. Now I'll just run over in a general sort of way, our policy in giving steroids to these patients. It's interesting that Dr. Guild in Baltimore feels strongly that bed rest is very important and she is apt to put her patients to bed and keep them there until their disease subsides. It may be a matter of months and often years that these patients stay in bed, and she's inclined to keep them on fairly strict isolation to avoid secondary infection. I can't go along with this because I think

that a child winds up after such treatment in psychological difficulties. What you gain physically, you may have lost by having a child who isn't able to face the normal rigors of existence in a world of healthy individuals. So, we don't do very much in the way of this kind of supportive treatment. We ask the parents please not to urge the children on to more activity than they want and usually when they're very edematous they don't want very much, but we usually don't lean over the other way and make the patient do a great deal of resting. We try to have him avoid, insofar as possible, exposure to people with colds. We don't have them put on a white gown, add mask precautions, or anything extreme. When actually receiving steroids, we have them on anti-bacterial treatment. We don't give it continuously. If we were to give it continuously, I'm a little afraid of building up resistant organisms, and I'd rather keep it in abeyance and save it for when the infections do occur. On the other hand, I treat infections much more readily than I would a normal patient, and just on suspicion we may start him on some kind of anti-bacterial treatment.

We don't do very much about diet, either. We avoid letting them eat potato-chips, peanuts, and that kind of salty food, but we don't put them on a really "no salt diet" because down the years it just hasn't seemed worth it. The child's appetite is usually capricious enough so it doesn't seem justifiable to spoil it further by taking salt completely away.

As I pointed out in my initial thoughts, we don't do much about differential diagnosis. After all, if a child has generalized edema, and proteinuria, there isn't any likely alternative diagnosis, as has been pointed out. We do like to prove it with chemistry because we're a teaching institution. But I think that's the only reason to do this.

Of course, if a patient has a positive Mantoux, we would do just as you did, put him on anti-tuberculous therapy and go ahead with steroid treatment. It's very important when you start your treatment to know what the Mantoux is, so you know whether you need to put him on the anti-tuberculous therapy or not. Oftentimes, particularly in older children with evidence of renal insufficiency, when you put them on steroids it will suppress renal function initially and you may get a rising BUN which can be alarming. I don't know whether this does them any real harm, but it scares me enough so I stop at that point, let them drop back to normal, and then try again later.

Blood pressure, even with the newer and fancy drugs that don't

have side-effects, is still something that has to be watched very carefully.

The sedimentation rate is a "poor man's electrophoresis" as far as I'm concerned; it correlates pretty well with what you see on electrophoresis. When the serum protein pattern is extremely abnormal, the sed-rate (we do the Westegren, which is an awfully simple way of doing it) will be extremely high. By this I mean 100, 120 or so, but as the protein pattern improves, it comes down, so I use this as a criterion as to how long treatment should be continued.

Now I would like to run over the type of treatment we use. My experience is greatest with prednisone. I've also been using all the others anybody would give me; as far as I can see though, I haven't a big enough series, nor is it controlled enough to speak with absolute authority; but my impression is that there is no real difference between prednisone, prednisolone, triamcinolone or the latest "dexa-methasone".

I think they all do about what is advertised they'll do if you give the recommended doses. With the "dexa-methasone" you give 1/10 of the dose you would with prednisone, but I can't see that this is any great advantage. I know a lot of people give nicely calculated doses of steroids, but in general, with these biological products, I think it makes little sense. Relatively speaking the majority of these children appear to tolerate much, much larger doses than adults. We have discovered down the ten years during use, that the larger the doses, the smaller the percentage of failures.

Whenever we begin to have trouble and are not getting the response we think we ought to, we raise the dosage. Even on a tiny child—perhaps if he were a year or so of age—I might start with 30 milligrams a day, but even on the small children (of 2 to 3 years) we can give them as much as 40 a day; then on larger ones, 60, and some of the much larger ones, around 80—even as much as 100 milligrams a day—depending on what their response is. We cover with an inexpensive anti-bacterial agent. I don't think there's much advantage in some of the mycins which are a good deal more expensive. If you do this, most of the children will diurese in about ten days to two weeks, and at about that time, the sed-rate will be on its way down toward normal, but it won't be normal. We keep on treating until the sed-rate is normal. At the end of three or four weeks, in most instances, this goal will be reached and the urine will have cleared of protein completely.

Of course when the children are in the process of diuresis, the protein level drops in the urine, largely by dilution, but when the diuresis is complete and they're beginning to concentrate again, in most instances, the protein remains absent. We check the blood pressure and BUN as frequently as we think we ought to. We had a couple of instances when diuresis was complicated by diarrhea. We got into serious electrolyte difficulties in these instances so now we make it a habit to give extra potassium at that time. Then after this initial treatment is over, we continue on a three-day-a-week routine, giving the same size doses that we give initially, and giving it three consecutive days each week. We teach the mother to test the urine for protein. We urge her to call us if there's any great jump in the amount of protein in which case we may raise the dose for three days, or even put them on a ten-day course again. From here on in, it's usually home treatment. We used to wait till proteinuria recurred before giving further treatment, but we found that such a high percentage of patients were relapsing that it seemed wiser to put them all on the scheduled treatment even though it might be unnecessary in some instances.

We put them on the drug on Tuesday, Wednesday, Thursday of each week and it's fascinating that with this we don't see any interference with growth, whereas in other cases where continuous medication is given, as in rheumatoid arthritis and that kind of thing, interference with growth has been quite a problem. Apparently letting them out from under the influence of hormone for four days each week allows the children to keep growing.

This isn't all perfect. We don't hit gold on every single patient. So what do you do if things aren't working? The first thing I think about is increasing the dosage. The next thing is possibly administering concentrated serum albumin if the patient is getting pretty uncomfortable. In some instances, this has apparently "tipped the scale" where the steroids had set the thing up ready to go and the serum albumin started the diuresis. Several patients have gone into a good remission and remained well thereafter.

Some people say that ACTH may work where the steroids fail. I haven't been too impressed with this fact, but in difficult cases, I try it from time to time. I do this with a double purpose in mind. One is that maybe the ACTH will work where the other has failed; if it doesn't the patient will be prepared for nitrogen-mustard as Dr. Clark West has written about. I prefer to have the adrenal in good working order and that's why I'm shifting from the steroid to ACTH to spruce the adrenal up before I go

to nitrogen-mustard which is the next thing in this treatment. Such treatment will sometimes "tip the scale" when others have failed.

We had a couple of children whom, after we tried everything else and had gotten nowhere, we sent home on the three-day-a-week program we didn't want to give up completely. Over a period of about 6 or 7 months, they lost their edema and are in generally good condition now, about 18 months later.

My view about the prognosis for a nephrotic patient has greatly brightened in the last 5 to 10 years. Instead of giving a "blood, sweat and tears" talk to the parents when I first meet them, I now give them a better than fighting chance that everything will go well and tell them if they follow the course most children do, things should be pretty easy to control and that although they'll be concerned about it for a good many years, the child probably won't actually be sick. The chances of his dying from this in the foreseeable future are not too great. Thus it certainly is a changed picture in the last 10 years.

QUERY: In our second case—the 13-year old boy who was seen in the clinic, we sent home. I cut his meticorten just the other day. His BUN, protein, etc., are prefectly normal. I had him on 10 milligrams of meticorten every other day, but there have been two things that have come up. This boy is in adolescence. He actually is in pubescence. He is getting acne and certain other changes. Now, according to your therapy, he should be on more meticorten, right?

DR. RILEY: More concentrated meticorten. I wouldn't give it every other day. I would give it three days in a row. I think you ought to treat well while you do and then stop altogether.

QUERY: Well, since he has done well on 10 milligrams every other day, would you still increase or concentrate him. In other words, is there any point in upping his dose now?

DR. RILEY: I would say from the way you describe his frequent relapses that I would feel more comfortable if I got him up to maybe 60 a day for three days a week because he has had a bad course on several occasions. I would be afraid that he's just playing possum on you now and I wouldn't trust him. Is he intelligent enough to do his own urine test?

QUERY: We check him once a week. . . .

DR. RILEY: Oh, you check him as often as once a week. Well, you might ride along then if you check that frequently. If he were able to do his own urine tests, we could let him go a month at a time; on the other hand, this takes a degree of intelligence that some of them may not have.

QUERY: Do you find or feel that if you use meticorten over an extended period of time, it's necessary to switch to ACTH?

DR. RILEY: We used to think that, but we have come to realize that what you are suppressing with the steroids is the whole pituitary-adrenal axis. If you give steroids, you suppress both the adrenal and the pituitary; if you give ACTH, you suppress the pituitary alone, and what you want functioning is the whole axis, therefore "waking up" the adrenal while you keep the pituitary suppressed, doesn't seem to me the logical thing to do. I think the general feeling is that the thing to do is taper off the dose so that the axis has to come back into the activity gradually rather than trying to help it along by giving ACTH.

QUERY: Do I understand you to say relapses have been more frequent since chemo-therapy has been started?

DR. RILEY: Yes.

QUERY: Is there any explanation for that?

DR. RILEY: My own explanation, whether it's correct or not, is that a lot of these patients would have died years ago; they wouldn't have had a chance to relapse. Now, we get them into a state of remission which is not too secure, but it's remission, and they're alive remissions instead of dead statistics.

QUERY: Is there any danger of the effect of steroid wearing off?

DR. RILEY: There doesn't seem to be. I have a couple of patients five years on this intermittent program and we still keep them under control. I think it's awfully important to emphasize that nobody should think of these drugs as being curative; they're simply suppressive, and what you're praying for is that the disease process will eventually burn itself out. Some of them burn themselves out pretty quickly apparently and with others, like a diabetic, you have to keep treating.

DR. WILSON: Did those die that were on steroids?

DR. RILEY: We haven't had any deaths in quite a while. The ones that have died are those that were hangovers from the earlier periods, didn't get their treatment started very early, and died of renal insufficiency, for the most part.

DR. WILSON: What has been the incidence of infections with steroids?

DR. RILEY: You mean associated with steroid therapy? Very little and easily recognizable. I don't think we've had a death on

steroids recently. Way back we had two deaths on steroids associated with infections. The first was where he was getting the acute treatment—that was many years back. He was getting smaller doses, he developed sepsis, which was easily recognized by fever, and the steroids were immediately stopped. He was put on all kinds of antibiotics. He died with sterile blood so I don't think you can say it was due to infection, but it shut his kidneys down. It looked as if we were able to control the infection even if we weren't able to control the results of the infection.

I think the other child was off steroids at the time, but had been on a good deal of steroids. He got a sudden overwhelming sepsis and died within a few hours of onset, so you could wonder if because of his suppressed pituitary adrenal axis, he wasn't able to rise to the occasion. Those are the only two I remember in our own group. That second type of death I would think we would have more of.

DR. JOYNER: How often do you see the thing that we used to see quite frequently, pneumococcal peritonitis? I saw one last week. . . .

DR. RILEY: Did you really? This business of keeping them edema-free apparently controls the infection problem and frequency of pneumococcus or other type of infection. It's not part of the picture. I think this is because they have to be in the edematous state to be so susceptible.

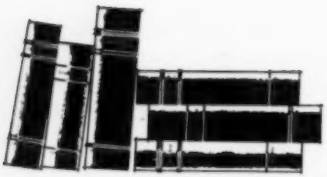
DR. JOYNER: One other thing, have you had much experience yourself with needle biopsy of the kidney?

DR. RILEY: No. I would love to do it. It's being done on a wholesale scale by a lot of braver people than I. Out in Minnesota, they biopsy everybody who turns up, so I'm waiting with interest for their findings.

QUERY: In these children that you have on your continuous high doses, if they develop hypertension you will reduce them won't you, to keep their hypertension down?

DR. RILEY: They haven't seemed to do that very much. If they get too tough for me, I'll put them on serpasil and other hypotensive agents.

DR. JOYNER: Thank you very much Dr. Riley. We've all enjoyed it and learned a great deal from it. On behalf of everyone, thank you for coming down. I hope you'll come back and see us again some time.



. . . Books

Edited by

MICHAEL A. BRESCIA, M.D.

Worth and Chavasse's "SQUINT", 9th edition. Baillière, Tindall and Cox, London, W.C.2., and the William Wilkins Co., Baltimore, Md., 1959. 392 pages, 214 illustrations. $10.00.

Claude Worth's "SQUINT" first appeared in 1903 and, for a period of 35 years in six subsequent editions, maintained its status as a classic on the etiology, pathology and treatment of this condition.

In a seventh edition Bernard Chavasse added as a subtitle "The Binocular Reflexes and the Treatment of Strabismus" and contributed new ideas as well as illustrative material on the development of binocular vision and on the etiology of squint.

As every pediatrician knows the objective in strabismus is to obtain not only an esthetic or cosmetic correction but also a physiologic result by preventing amblyopia (blunt vision) in the deviating eye and by effecting the use of both eyes together as a team (for binocular single vision).

Lyle and Bridgeman, the authors of the present edition, present in an interesting and practical manner consecutive chapters on the anatomical and physiologic basis of binocular vision, on the structural development of the eyes and orbit in the child, on reflex development in the child, on the site and nature of obstacles in the reflex paths, on accommodational and other types of squint primarily related to the state of refraction, on heterophoria, on inhibitions and their sequels, on binocular vision and retinal correspondence, on methods of investigation, on general principles in the treatment of strabismus, on ocular palsy and its treatment, on the clinical classification of squint, on the medical and surgical treatment of and on the prognosis of convergent, or divergent and of vertical squint, and on the incidence and theories of the causation of squint.

To the pediatrician the following chronologic table of development will prove particularly informative:

At birth: Ocular movements are aimless. *At 2 weeks*: Some convergence elicited. *At 5 to 6 weeks*: Stares at large objects. *At*

2 months: Eyes follow a person or hand. *At 3 months*: Eyes follow a moving pencil. *At 4 months*: Head is held up, and an object is reached for. *At 6 months*: Body follows head and eyes to extent of sitting up and the convergence is prolonged and sustained. *At 12 months*: Erect posture is attempted. *At 13 months*: Points to nose and eyes. *At 2 years*: Vision = 6/12, extreme convergence is maintained and reflexes are capable of extinction. *At 3 years*: Vision = 6/9, and reflexes are grounded but would suffer from disuse. *At 4 years*: Reflexes are grounded, and disuse results in deterioration but not in extinction but re-use causes rapid recovery. *At 5 years*: Vision = 6/6 and reflexes are fixed but are capable of deterioration from disuse. *At 8 years*: Reflexes are unconditionally fixed and the period of flux is ended.

It is pointed out that the factors facilitating the development of conditioned binocular reflexes are the very factors that have to be considered in planning treatment to restore binocular single vision. In addition to sufficient structural development these factors include the ability to learn, alertness, the absence of distracting influences and simplicity and reinforcement of stimuli.

Although this book was written primarily for the opthalmologist, the practitioners of many other branches of the profession will derive much information and pleasure from its text and its illustrations. It is not only well written but also beautifully illustrated and covers the entire subject thoroughly. It is highly recommended.

JOSHUA ZUCKERMAN, M.D.

THE MIDDLE EAR, by Heinrich G. Kobrak, M.D., Ph.D., with a foreword by John R. Lindsay, M.D. Cloth, 254 pp., price $15.00. Chicago, The University of Chicago Press, 5750 Ellis Ave., Chicago 37, Ill., 1958.

The text is an outstanding comprehensive presentation and review of the middle ear. Recent advances in otologic surgical technique demand an understanding of the anatomy, physiology and bioacoustics of the middle ear. Beginning with a description of the structure and function of the middle ear, Dr. Heinrich G. Kobrak, Professor of Otologic Research at the College of Medicine, Wayne State University, until the time of his death in November 1957, establishes this firm foundation for the reader.

The contributions of Lindsay, Rosen, Wullstein, Zoellner—four surgeons intimately identified with recent advances in otologic surgery—offer a basic understanding of surgical treatment.

This text is a valuable guidebook to all individuals concerned with the problem of middle ear disease, deafness and treatment in adults and children. A. SHULMAN, M.D.

SLOBODY, LAWRENCE B., M.D.: *"Survey of Clinical Pediatrics"*—Third Edition. McGraw-Hill Book Co., Inc., New York (The Blakiston Division) 1959. $11.00.

This is the third edition of what has become a standard and deservedly popular text of pediatrics. Extensive revisions have been made and new material incorporated, as well as additions to the previous text. Among the changes are a complete revision of the approach to congenital heart disease, the inclusion of additional information about nutritional requirements, abnormal hemoglobin and psychosocial development. The introduction of newer antibiotics, steroids and psychotherapeutic agents, brings this subject matter up to date. ECHO and adeno virus diseases are welcome additions.

The author possesses a singular ability of presenting material in succinct form without becoming didactic. The book could well be on every pediatrician's desk for rapid reference and it is obviously of great value to the resident or medical student either for continuous reading or for refreshing his knowledge on individual subjects.

This new "Survey" cannot be too highly recommended.

JOHN FITCH LANDON, M.D.

Embryonic Nutrition. Edited by DOROTHEA RUDNICK. Cloth. Pp. 113. Price $3.25. The University of Chicago Press, Chicago, 1958.

This small volume is one of a series of books issued as a result of the Developmental Biology Conference Series, 1956, held under the auspices of the National Academy of Sciences. This particular volume contains the papers and discussions that were read at Brown University, July 23-24, 1956. These papers do not hold any immediate clinical interest. However, this is the kind of research that eventually bears useful clinical material and those who wish to delve in some fundamental research would find these papers of interest. The papers contained in this volume are as follows: Embryonic Energy Exchange by E. J. Boell; Metabolic Patterns in the Sea-Urchin Embryo by J. Lee Kavanau; Yolk Utilization in Fishes by Sydney Smith; Antigens as Tracers of Embryonic Synthesis by James D. Ebert; Nutrient Necessities in Chick Development by Nelson T. Spratt, Jr. and Enzymes: Formation and Growth by Florence Moog. M. A. B.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